HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 223-231. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 8th June, 2016, Accepted, 12th July, 2016, Published online, 3rd August, 2016
DOI: 10.3987/COM-16-S(S)7

[3+2] CYCLOADDITIONS OF *N*-PROTECTED '(*S*)-DIAZOPROLINE' WITH SELECTED ACETYLENES

Grzegorz Mlostoń,[a]* Paulina Pipiak,[1,a] and Heinz Heimgartner[b]*

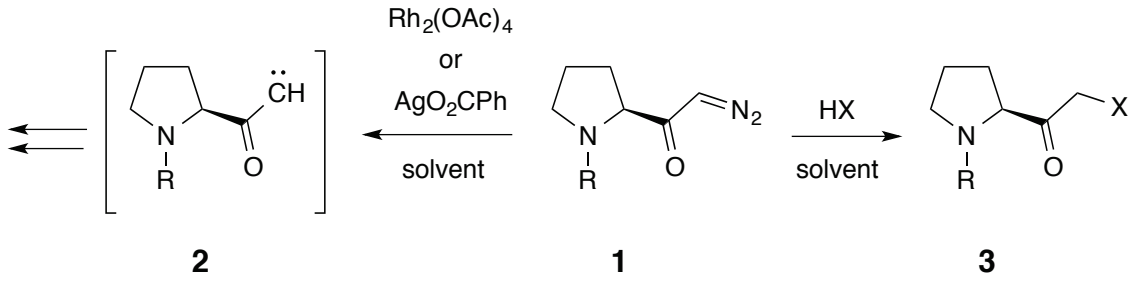
a: Department of Organic and Applied Chemistry, University of Łódź, Tamka 12, PL-91-403 Łódź, Poland; e-mail: gmloston@uni.lodz.pl
b: Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland; e-mail: heinz.heimgartner@chem.uzh.ch

Dedicated to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

Abstract – Acetylene carboxylates and an acetylene phosphonate reacted with *N*-protected (*S*)-2-(diazoacetyl)pyrrolidines ((*S*)-diazoprolines) to give optically active bis-heterocyclic pyrazole derivatives in a regioselective [3+2] cycloaddition. The reactions occurred at 60 °C in THF solution in the absence of a catalyst. However, diethyl ethynylphosphonate reacted significantly slower than the carboxylates. The obtained products were shown to exist in $CDCl_3$ solution at room temperature as mixtures of rotamers. The reactions of diethyl ethynylphosphonate with a selected cyclic α-oxodiazo compound, i.e. 2-diazoacenaphthen-1-one, yielded a fused tricyclic pyrazole derivative.

INTRODUCTION

Diazo compounds bearing an α-oxo group are well known as versatile reagents applied as precursors of α-oxocarbenes and as 1,3-dipoles in [3+2] cycloadditions with diverse dipolarophiles.[2] Interesting representatives of α-oxodiazo compounds are *N*-protected (*S*)-2-(diazoacetyl)pyrrolidines **1** ('(*S*)-diazoprolines'), which are easily available from *N*-protected (*S*)-proline.[3] Hitherto, the most relevant applications of diazoprolines **1** comprise their decomposition with elimination of N_2 leading either to α-oxocarbenes **2** (metal catalyst)[4] or the α-haloketones by treatment with HX reagents (Scheme 1).[5]



2 **1** **3**

Scheme 1

It is well known that in catalyst-free reactions of α-oxodiazo compounds such as α-diazoesters, reactions with both electron-deficient and electron-rich acetylenes lead to pyrazoles.[6] However, cyclic α-diazo ketones react with acetylenes to yield fused polycyclic pyrazole derivatives via ring enlargement of the initially formed spirocyclic 3*H*-pyrazol.[6]

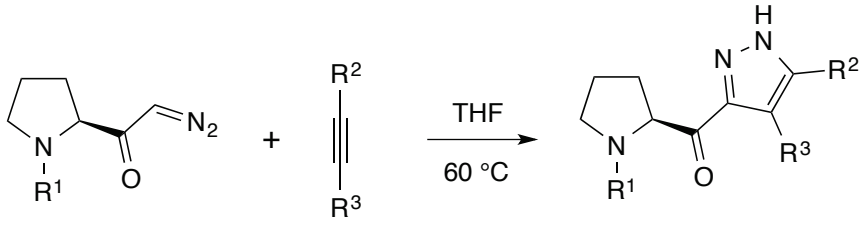
Syntheses of phosphonylated pyrazoles and related phosphorus-containing heterocycles have been reviewed recently.[7] Only one report on the [3+2] cycloaddition of an acetylene phosphonate with diazomethane is known leading to a 3-phosphonylated pyrazole in low yield.[8]

Surprisingly little is known on the application of diazoprolines in [3+2] cycloadditions. In a recent publication we described reactions of some aryl and hetaryl thioketones with *N*-protected diazoprolines **1** leading to optically active α,β-unsaturated pyrrolidine ketones via the so-called 'two-fold extrusion mechanism'.[9]

The goal of the present study was the examination of [3+2] cycloadditions of *N*-benzoyl- and *N*-(*tert*-butyloxy)carbonyl-protected (*S*)-2-(diazoacetyl)pyrrolidines, **1a** and **1b**, respectively, with selected electron deficient dipolarophiles.

RESULTS AND DISCUSSION

Three electron-deficient acetylenes, namely dimethyl acetylenedicarboxylate (DMAD, **4a**), methyl propiolate (MP, **4b**), and diethyl ethynylphosphonate (**4c**), were selected for the reaction with **1a** and **1b**. To the best of our knowledge, **4c** has never been used in a [3+2] cycloaddition with diazo compounds. In a test experiment, *N*-benzoyl-diazoproline **1a** was reacted with two mol-equivalents of **4a** in THF solution at 60 °C. After 2 h, the reaction was complete, and after chromatographic workup, a single product was obtained in 95% yield. The ^{1}H-NMR spectrum of the product showed two singlets of two MeO groups at 3.84 and 3.89 ppm as well as a broad singlet for HC(2) of the pyrrolidine moiety at 6.00 ppm. The latter group absorbed in the ^{13}C-NMR spectrum at 62.0 ppm. The mass spectrum confirmed the structure of the cycloadduct **5a**[10] (Scheme 2, Table) by the presence of $[M+1]^{+}$ at m/z = 386.



1 **4** **5**

Scheme 2

The analogous experiment with **1b** and **4a** gave the expected cycloadduct **5d**, which was isolated in 91% yield. In that case, the ^{1}H-NMR spectrum registered at room temperature revealed the presence of two rotamers about the N–CO bond in a ratio of 75:25.

Table. Synthesis of (*S*)-3-(pyrrolidine-2-carbonyl)-1*H*-pyrazoles **5**[a)]

1	R^1	**4**	R^2	R^3	**5**	Yield (%)[b)]
a	Bz	**a**	CO_2Me	CO_2Me	**a**	95
a	Bz	**b**	CO_2Me	H	**b**	90
a	Bz	**c**	$PO(OEt)_2$	H	**c**	71
b	Boc	**a**	CO_2Me	CO_2Me	**d**	91
b	Boc	**b**	CO_2Me	H	**e**	78
b	Boc	**c**	$PO(OEt)_2$	H	**f**	84

[a)] For reaction conditions see Scheme 2. [b)] Yield of isolated product.

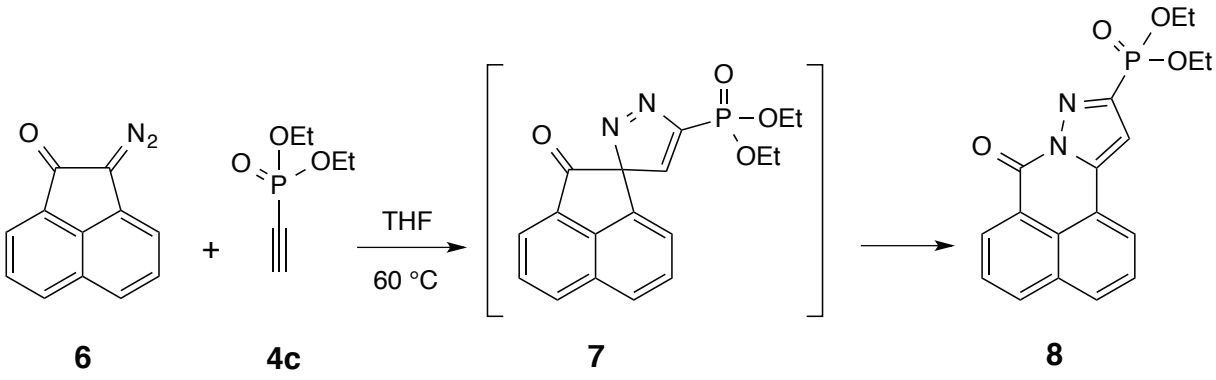
The reaction of **1a** with **4b** was significantly slower, and the TLC analysis indicated its completion only after 7 h. The expected structure **5b** of the product was confirmed by mass spectrometry ($[M+1]^+$ at m/z = 328). The cycloaddition occurred regioselectively, and the structure of **5b** was elucidated by ^{13}C-NMR spectroscopy. The characteristic absorption of HC(4) of the pyrazole ring appeared at 110.0 ppm, in good agreement with the data reported for diethyl 1*H*-pyrazole-3,5-dicarboxylate.[6] In contrast to **5a**, the ^{1}H-NMR spectrum in $CDCl_3$ at room temperature evidenced the presence of two rotamers of the product in a 91:9 ratio. Similarly, the sole product obtained from the reaction of **1b** with **4b** was identified as a 53:47 mixture of two rotamers of the analogous regioisomer **5e**.

The least reactive dipolarophile was **4c**, and its reaction with **1a** required 55 h at 60 °C for its completion. The only product formed was **5c**, isolated in 71% yield. The ^{1}H-NMR spectrum at room temperature indicated that two rotamers in a ratio of 85:15 were present. The ^{13}C-NMR spectrum showed the doublet

for HC(4) at 113.3 ppm with $^2J_{P,C}$ = 18.6 Hz, proving the structure of the pyrazole-3-phosphonate **5c**. The analogous cycloadduct **5f** with the *N*-Boc protecting group was obtained in 84% yield after 72 h. Similarly to **5c**, the ^{1}H-NMR spectrum showed the existence of two rotamers.

In the case of **5e**, the ^{1}H-NMR spectrum was also registered in 1,1,2,2-tetrachloroethane-D_2 at 50 and 80 °C. At the latter temperature, only one set of signals was observed, indicating that the coalescence of the two rotamers was achieved. The presence of two rotamers in solutions of **5c** and **5f** was also observed in the ^{31}P-NMR spectra at room temperature. Whereas in **5c** two signals appeared at 6.22 and 5.68 ppm for the major and minor rotamer, respectively, the corresponding signals in the case of **5f** were found at 5.55 and 5.74 ppm.

In extension of the study, the reaction of **4c** with a cyclic α-oxodiazo compound, i.e. 2-diazoacenaphthen-1-one (**6**), was investigated. Some reactions of DMAD with cyclic α-oxodiazo compounds of type **6** were reported to deliver polycyclic, fused heterocycles derived from isoquinolin-7-one.[12] The postulated reaction pathway involves the [3+2]-cycloaddition reaction, leading initially to spiro-pyrazoles of type **7**, which subsequently undergo a spontaneous 1,5-sigmatropic migration of the carbonyl group, i.e. a ring expansion, yielding isoquinolin-7-ones of type **8** as the final products.[12] In our study, the slow reaction of 2-diazoacenaphthen-1-one (**6**) with diethyl ethynyl-phosphonate (**4c**) was carried out at 60 ºC for 50 h. The only product found in the reaction mixture was identified as the polycyclic phosphonate **8**, isolated after chromatography in 83% yield (Scheme 3).



6 **4c** **7** **8**

Scheme 3

The structure of **8** was elucidated based on the spectroscopic data. Thus, in the ^{1}H-NMR spectrum ($CDCl_3$), a characteristic singlet at 7.47 ppm was attributed to the HC(4) of the pyrazole ring. In addition, the ^{13}C-NMR spectrum showed the doublet for HC(4) at 107.8 ppm with $^2J_{P,C}$ = 24.5 Hz, which proves the postulated structure of the fused pyrazole-3-phosphonate **8**. Finally, in the ^{31}P-NMR spectrum, the signal of the P-atom was found as a singlet located at 8.79 ppm.

CONCLUSIONS

The present study showed that *N*-protected (*S*)-diazoprolines **1** react with acetylene carboxylates and an acetylene phosphonate to give optically active pyrazole-3-carboxylates and 3-phosphonates, respectively, in a regioselective manner. The experiments showed that acetylene carboxylates react significantly faster than the phosphonate. However, in all cases, the yield of the isolated product was high. In general, the obtained bis-heterocyclic compounds **5** exist in $CDCl_3$ solution at room temperature as mixtures of two rotamers, and the coalescence temperature for the phosphonate **5e** was observed at ca. 80 °C. The reaction of diethyl ethynylphosphonate (**4c**) with the cyclic α-oxodiazo compound **6** showed that in analogy to acetylene carboxylates[6] a tricyclic fused pyrazole phosphonate was formed. These hitherto unknown compounds are of interest as potentially biologically active compounds.

EXPERIMENTAL

General remarks. Melting points were determined in a capillary using a Melt-Temp. II (Aldrich) apparatus, and they are uncorrected. The IR spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions in cm^{-1}. The ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were measured on a Bruker Avance III instrument (600, 150, and 243 MHz, resp.) in $CDCl_3$ using solvent signals as reference. Chemical shifts (δ) are given in ppm and coupling constants *J* in Hz. ESI-MS were recorded on a Varian 500-MS LC IonTrap spectrometer in the Laboratory of Mass Spectrometry of the University of Łódź. Elemental analyses were performed in the Laboratory of the Faculty of Chemistry (University of Łódź). Optical rotations: Perkin-Elmer 241 MC polarimeter, in CH_2Cl_2 at 20 ºC.

Starting materials. (*S*)-1-(1-Benzoylpyrrolidin-2-yl)-2-diazoethanone (**1a**) and *tert*-butyl (*S*)-2-(diazoacetyl)pyrrolidine-1-carboxylate (**1b**) were prepared as described in refs.[4c,5a] 2-Diazoacenaphthen-1-one (**6**) was obtained by oxidation of acenaphthenequinone hydrazone with oxalyl chloride according to a literature protocol.[13] Diethyl ethynylphosphonate (**1c**) was prepared according to a modified literature procedure.[14] Other reagents used in the present study were commercially available. Reported yields refer to isolated products.

General procedure for the reaction of diazo compounds 1 and 6 with alkynes 4. The corresponding diazo compound (**1a–b** or **6**; 0.5 mmol) and alkyne (**4a–c**; 1 mmol) were placed in a pressure tube (in the cases of **1a** and **6**, the mixture was dissolved in 0.5 mL freshly distilled THF; for **1b**, substrates were placed in a pressure tube without solvent (neat)). The reaction mixture was magnetically stirred at 60 ºC (oil bath), and the progress of the reaction was monitored by TLC (SiO_2 plates, AcOEt). Then, the solvent was evaporated and the solid product was purified by column chromatography (CC). For compounds **5b–c**, **5e–f** the ^{1}H-NMR spectra were registered at 23 °C, 50 °C and 80 °C in

1,1,2,2-tetrachloroethane-D_2.

(*S*)-Dimethyl 3-(1-benzoylpyrrolidine-2-carbonyl)-1*H*-pyrazole-4,5-dicarboxylate (5a). The reaction of **1a** with **4a** was complete after 2 h. Then, the solvent was evaporated, and the crude product was purified by CC (AcOEt/CH_2Cl_2 1:1). Yield: 186 mg (95%). Pale yellow crystals, mp 82–84 °C. ^{1}H-NMR: 1.91–2.05 (*m*, 3H, CH_2CH_2); 2.44–2.47 (*m*, 1H, CH_2CH_2); 3.61–3.75 (*m*, 2H, CH_2N); 3.84 (*s*, 3H, CO_2Me); 3.89 (*s*, 3H, CO_2Me); 6.00 (br.*s*, 1H, CHN); 7.44–7.47 (m, 3 arom. CH); 7.65–7.67 (m, 2 arom. CH). ^{13}C-NMR: 24.9 (CH_2); 29.3 (CH_2); 50.6 (CH_2); 52.2 (Me); 52.6 (Me); 62.0 (CH); 127.2, 128.3, 130.3 (5 arom. CH); 136.0 (arom. C); 117.9, 133.5, 145.5 (3 C(pyrazole)); 157.7, 163.7, 169.7, 191.0 (4 C=O). IR (KBr): 2954*w*, 1740*s*, 1611*s*, 1575*m*, 1449*s*, 1295*m*, 1227*m*, 1124*m*, 982*w*, 727*w*. ESI-MS: 386 ([*M*+1]$^+$, 35), 408 ([*M*+23]$^+$, 100), 424 ([*M*+39]$^+$, 65). $[\alpha]^{25}_D$ –42.0 (*c* 0.5; CH_2Cl_2). Anal. Calcd for $C_{19}H_{19}N_3O_6$ (385.37): C 59.22, H 4.97, N 10.90. Found: C 59.12, H 4.97, N 10.76.

(*S*)-Methyl 3-(1-benzoylpyrrolidine-2-carbonyl)-1*H*-pyrazole-5-carboxylate (5b). The reaction of **1a** with **4b** was complete after 7 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt). Compound **5b** consisted of a ca. 91:9 mixture of two rotamers. Yield: 151 mg (90%). Colorless crystals, mp 62–64 °C. ^{1}H-NMR (values for the minor rotamer in italics): 1.97–2.07 (*m*, 3H, CH_2CH_2); 2.44 (br.*s*, 1H, CH_2CH_2); 3.65–3.77 (*m*, 2H, CH_2N); 3.95 (*s*, 3H, CO_2Me); 5.71, *5.24* (br.*s*, 1H, CHN); 7.45–7.46 (*m*, 3 arom. CH); 7.33 (br.*s*, =CH), 7.63–7.64 (*m*, 2 arom. CH); 11.90 (br.*s*, 1H, NH). ^{13}C-NMR: 25.3 (CH_2); 29.4 (CH_2); 50.4 (CH_2); 52.2 (Me); 62.2 (CH); 110.0 (CH=); 127.3, 128.2, 130.2 (5 arom. CH); 136.1 (arom. C); 137.2, 147.0 (2 C(pyrazole)); 159.7, 169.6, 190.4 (3 C=O). IR: 2976*w*, 1734*s*, 1699*s*, 1612*s*, 1575*m*, 1448*s*, 1314*m*, 1234*s*, 1012*w*, 717*w*. ESI-MS: 328 ([*M*+1]$^+$, 100), 350 ([*M*+23]$^+$, 93). $[\alpha]^{25}_D$ –23.4 (*c* 1.0; CH_2Cl_2). Anal. Calcd for $C_{17}H_{17}N_3O_4$ (327.33): C 62.38, H 5.23, N 12.84. Found: C 62.19, H 5.22, N 12.60.

(*S*)-Diethyl 3-(1-benzoylpyrrolidine-2-carbonyl)-1*H*-pyrazole-5-phosphonate (5c). The reaction of **1a** with **4c** was complete after 55 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt). Compound **5c** consisted of a ca. 85:15 mixture of two rotamers. Yield: 140 mg (71%). Colorless crystals, mp 53–55 °C. ^{1}H-NMR (values for the minor rotamer in italics): 1.24–1.29 (*m*, 6H, 2 OCH_2*Me*); 1.86–1.97 (*m*, 3H, CH_2CH_2); 2.38–2.41 (*m*, 1H, CH_2CH_2); 3.54–3.67; *3.80–3.82* (*m*, 2H, CH_2N); 4.05–4.14 (*m*, 4H, O*C*H_2Me); 5.70, *5.37* (br.*s*, 1H, CHN); 7.31–7.35 (*m*, 3 arom. CH); 7.53–7.54 (*m*, 2 arom. CH); 13.43 (br.*s*, 1H, NH). ^{13}C-NMR: 16.1, *16.2* (2*d*, $^3J_{P,C}$ = 6.3 Hz, 2 OCH_2*Me*); 25.4 (CH_2); 29.5 (CH_2); 50.3 (CH_2); 62.4 (CH); 63.3, *63.4* (2d, $^2J_{P,C}$ = 7.5 Hz, 2 O*C*H_2Me); 113.3 (*d*, $^2J_{P,C}$ = 18.6 Hz, CH); 127.3, 128.1, 130.0 (5 arom. CH); 136.3 (arom. C); 148.6 (br.), 134.1 (br., 2 C(pyrazole)); 169.2, 191.9 (2

C=O). ^{31}P-NMR (value for the minor rotamer in italics): 6.22, *5.68*. IR (KBr): 3115*m*, 2987*m*, 1699*s*, 1630*s*, 1448*s*, 1237*s*, 1142*m*, 1023*s*, 978*m*, 759*m*, 702*m*, 606*m*. ESI-MS: 406 ([*M*+1]$^+$, 55), 428 ([*M*+23]$^+$, 100). $[\alpha]^{25}_D$ –17.4 (*c* 1.0; CH_2Cl_2). Anal. Calcd for $C_{19}H_{24}N_3O_5P$ (405.38): C 56.29, H 5.97, N 10.37. Found: C 56.12, H 6.08, N 10.24.

(*S*)-Dimethyl 3-[1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl]-1*H*-pyrazole-4,5-dicarboxylate (5d). The reaction of **1b** with **4a** was complete after 2 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt/hexane 1:1). Compound **5d** consisted of a ca. 75:25 mixture of two rotamers. Yield: 176 mg (91%). Colorless crystals, mp 76–78 °C. ^{1}H-NMR (values for the minor rotamer in italics): *1.27*, 1.54 (*s*, 9H, *t*Bu); 1.89–2.02 (*m*, 3H, CH_2CH_2); 2.31–2.33 (*m*, 1H, CH_2CH_2); 3.46–3.62 (*m*, 2H, CH_2N); 3.85, *3.92*, *3.96* (3*s*, 6H, CO_2Me); 5.61, *5.13* (br.*s*, 1H, CHN); 13.61 (br.*s*, 1H, NH). ^{13}C-NMR: 23.7 (CH_2); 28.4 (Me_3C); 29.7 (CH_2); 47.1 (CH_2); 52.1 (Me); 52.5 (Me); 61.7 (CH); 80.7 (Me_3C); 118.2, 132.8 (br.), 145.5 (br., 3 C(pyrazole)); 155.1, 157.5, 163.8, 191.9 (4 C=O). IR (KBr): 3157*m*, 2978*m*, 2957*m*, 1733*s*, 1705*s*, 1667*s*, 1570*w*, 1436*s*, 1368*m*, 1267*s*, 1163*s*, 1127*s*, 1041*m*, 981*m*, 894*w*, 749*w*. ESI-MS): 404 ([*M*+23]$^+$, 100). $[\alpha]^{25}_D$ –84.6 (*c* 1.0; CH_2Cl_2). Anal. Calcd for $C_{17}H_{23}N_3O_7$ (381.38): C 53.54, H 6.08, N 11.02. Found: C 53.53, H 6.03, N 10.93.

(*S*)-Methyl 3-[1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl]-1*H*-pyrazole-5-carboxylate (5e). The reaction of **1b** with **4b** was complete after 12 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt). Compound **5e** consisted of a ca. 53:47 mixture of two rotamers. Yield: 127 mg (78%). Colorless crystals, mp 67–69 °C. ^{1}H-NMR (values for the minor rotamer in italics): *1.19*, 1.43 (*s*, 9H, *t*Bu); 1.88–1.99 (*m*, 3H, CH_2CH_2); 2.25–2.30 (*m*, 1H, CH_2CH_2); 3.44–3.60 (*m*, 2H, CH_2N); 3.86, *3.90* (*s*, 3H, CO_2Me); 5.33, *5.00* (*s*, 1H, CHN); 7.17, *7.20* (*s*, 1H, =CH); 11.97 (br.*s*, 1H, NH). ^{13}C-NMR: 24.1 (CH_2); 28.4 (Me_3C); 30.9 (CH_2); 47.0 (CH_2); 52.1 (Me); 61.9 (CH); 80.2 (Me_3C); 109.9 (CH=); 138.1 (br.), 146.8 (br., 2 C(pyrazole)); 160.2, 154.8, 192.7 (3 C=O). IR (KBr): 3145*m*, 2978*m*, 1736*s*, 1702*s*, 1559*w*, 1414*s*, 1367*m*, 1311*w*, 1234*s*, 1163*s*, 1129*m*, 1012*w*, 859*w*, 772*w*. ESI-MS: 346 ([*M*+23]$^+$, 100). $[\alpha]^{25}_D$ –47.6 (*c* 1.0; CH_2Cl_2). Anal. Calcd for $C_{15}H_{21}N_3O_5$ (323.34): C 55.72, H 6.55, N 13.00. Found: C 55.64, H 6.58, N 12.88.

(*S*)-*tert*-Butyl 2-[5-(diethoxyphosphoryl)-1*H*-pyrazole-3-carbonyl]pyrrolidine-1-carboxylate (5f). The reaction of **1b** with **4c** was complete after 72 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt). Compound **5f** consisted of a ca. 51:49 mixture of two rotamers. Yield: 170 mg (84%). Colorless crystals, mp 94–96 °C. ^{1}H-NMR (values for the minor rotamer in italics): 1.24, *1.46* (br.*s*, 9H, *t*Bu); 1.33–1.35 (*m*, 6H, 2 OCH_2Me); 1.87–1.97 (*m*, 3H, CH_2CH_2); 2.32–2.37 (*m*, 1H,

CH_2CH_2); 3.47–3.65 (*m*, 2H, CH_2N); 4.10–4.21 (*m*, 4H, 2 O*C*H_2Me); 5.26, *5.40* (br.*s*, 1H, CHN); *7.21*, 7.22 (br.*s*, 1H, =CH). ^{13}C-NMR: 16.1–16.2 (*m*, OCH_2*Me*); 23.7 (CH_2); 28.1 (*Me*$_3$C); 30.9 (CH_2); 46.7 (CH_2); 62.1 (CH); 63.3–63.4 (*m*, O*C*H_2Me); 79.6 (Me_3*C*); 112.8 (*d*, $^2J_{C,P}$ = 18.6, =CH); 134.3 (br.), 148.5 (br., 2 C(pyrazole)); 153.8, 193.7 (2 C=O). ^{31}P-NMR (value for the minor rotamer in italics): 5.55, *5.74*. IR (KBr): 3115*m*, 2981*m*, 2935*m*, 1701*s*, 1405*s*, 1366*m*, 1234*s*, 1165*s*, 1027*s*, 976*m*, 956*m*, 795*w*, 603*w*. ESI-MS: 424 ([*M*+23]$^+$, 100). $[\alpha]^{25}_D$ –18.6 (*c* 1.0; CH_2Cl_2). Anal. Calcd for $C_{17}H_{28}N_3O_6P$ (401.39): C 50.87, H 7.03, N 10.47. Found: C 50.74, H 7.01, N 10.37.

Diethyl 7-oxo-7*H*-benzo[*de*]pyrazolo[5,1-*a*]isoquinoline-10-phosphonate (8). The reaction of **6** with **4c** was complete after 50 h. The solvent was evaporated, and the crude product was purified by CC (AcOEt). Yield: 174 mg (83%). Fluorescent yellow crystals, mp 143–144 °C. ^{1}H-NMR {^{31}P}: 1.44 (*t*, $^3J_{H,H}$ = 7.2 Hz, 6H, 2 OCH_2*Me*); 4.35 (*q*, $^3J_{H,H}$ = 7.2 Hz, 4H, 2 O*C*H_2Me); 7.47 (*s*, 1H, =CH); 7.77 (*t*, $^3J_{H,H}$ = 7.8 Hz, 1 arom. CH); 7.86–7.88 (*m*, 1 arom. CH); 8.11 (*d*, $^3J_{H,H}$ = 8.4 Hz, 1 arom. CH); 8.18 (*d*, $^3J_{H,H}$ = 7.2 Hz, 1 arom. CH); 8.33 (*d*, $^3J_{H,H}$ = 7.8 Hz, 1 arom. CH); 8.92 (*d*, $^3J_{H,H}$ = 7.2 Hz, 1 arom. CH). ^{13}C-NMR: 16.1 (*d*, $^3J_{C,P}$ = 6.5 Hz, OCH_2*Me*); 63.0 (*d*, $^2J_{C,P}$ = 6.0 Hz, O*C*H_2Me); 107.8 (*d*, $^2J_{C,P}$ = 24.5 Hz, =CH); 119.3, 122.2, 125.0 (3 arom. C); 125.2, 126.8, 126.9, 130.5, 132.5, 135.6 (6 arom. CH); 131.7 (1 CH(pyrazole)); 142.6 (*d*, $^3J_{C,P}$ = 10.0 Hz, 1 C(pyrazole)); 148.3 (*d*, $^1J_{C,P}$ = 231.0 Hz, 1 C(pyrazole)); 157.3 (C=O). ^{31}P-NMR: 8.79. IR (KBr): 3104*w*, 2984*w*, 1717*s*, 1597*w*, 1578*w*, 1559*w*, 1505*w*, 1287*m*, 1261*s*, 1236*m*, 1068*m*, 1027s, 979*m*, 903*m*, 770*m*. Anal. Calcd for $C_{18}H_{17}N_2O_4P$ (356.31): C 60.68, H 4.81, N 7.86. Found: C 60.45, H 4.89, N 7.67.

Temperature dependent ^{1}H-NMR spectra for selected products 5. Solutions of products **5b–c** and **5e–f** in $C_2D_2Cl_4$ were registered at 23 °C, 50 °C, and 80 °C, respectively. In the case of **5e** the coalescence temperature was observed < 80 °C. In another cases signals of two rotamers were observed even at 80 °C.

(*S*)-Methyl 3-[1-(*tert*-butoxycarbonyl)pyrrolidine-2-carbonyl]-1*H*-pyrazole-4-carboxylate (5e). ^{1}H-NMR ($C_2D_2Cl_4$) (at 80 °C): 1.39 (*s*, 9H, *t*Bu), 1.92–2.02 (*m*, 3H, CH_2CH_2), 2.29–2.38 (*m*, 1H, CH_2CH_2), 3.55–3.62 (*m*, 2H, CH_2N), 3.98 (*s*, 3H, CO_2Me), 5.16 (br.*s*, 1H, CHN), 7.33 (*s*, 1H, NH).

ACKNOWLEDGEMENTS

The authors thank the National Science Center (PL-Cracow) for financial support within the project *Maestro* (Grant Maestro-3; Dec-2012/06/A/ST5/00219).

REFERENCES AND NOTES

1. Part of the planned PhD Thesis of *P. P.*, University of Łódź.
2. a) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091; b) N. R. Candeias, R. Paterna, and P. M. P. Gois, *Chem. Rev.*, 2016, **116**, 2937.
3. P. Pipiak and G. Mlostoń, *Chem. Heterocycl. Compd.*, 2016, **52**, 146.
4. a) A. Padwa, D. C. Dean, and L. Zhi, *J. Am. Chem. Soc.*, 1989, **111**, 6451; b) A. Padwa, D. C. Dean, and L. Zhi, *J. Am. Chem. Soc.*, 1992, **114**, 593; c) S. Abele, K. Voegtli, and D. Seebach, *Helv. Chim. Acta*, 1999, **82**, 1539; d) S. Hanessian and A. K. Chattopadhyay, *Org. Lett.*, 2014, **16**, 232.
5. a) S. N. Lakeev, I. Z. Mullagalin, F. Z. Galin, I. O. Maidanova, and M. F. Abdullin, *Russ. Chem. Bull.*, 2002, **51**, 2230; b) F. Bures and J. Kulhanek, *Tetrahedron: Asymmetry*, 2005, **16**, 1347; c) N. Vishwanathaa and V. V. Sureshbabu, *Prot. Pept. Lett.*, 2012, **19**, 308.
6. D. Vuluga, J. Legros, B. Crousse, and D. Bonnet-Delpon, *Green Chem.*, 2009, **11**, 156.
7. T. E. Ali and S. M. Abdel-Kariem, *Heterocycles*, 2012, **85**, 2073.
8. B. C. Saunders and P. Simpson, *J. Chem. Soc.*, 1963, 3351.
9. G. Mlostoń, P. Pipiak, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, 2015, **98**, 190.
10. Tautomerism of pyrazole derivatives is a complex problem, which has been discussed in numerous publications[11] based on both experimental data and computational methods. We are aware of the fact that an equilibrium may exist in solutions of the prepared pyrazoles **5**. However, there was only one tautomer found in each of the registered ^{1}H-NMR spectra. For that reason, we attributed tentatively structure **5** for all of the isolated products.
11. a) B. Stanovnik and J. Svete, in 'Science of Synthesis', Vol. 12, ed. by R. Neier, George Thieme Verlag, Stuttgart, 2002, Chapter 12.1, pp. 15–227; b) D. Tarabova, S. Soralova, M. Breza, M. Fronc, W. Holzer, and V. Milata, *Beilstein J. Org. Chem.*, 2014, **10**, 752.
12. a) S.-J. Chang, B. K. R. Shankar, and H. Shechter, *J. Org. Chem.*, 1982, **47**, 4226; b) P. A. Blair, S.-J. Chang, and H. Shechter, *J. Org. Chem.*, 2004, **69**, 7123.
13. M. I. Javed and M. Brewer, *Org. Lett.*, 2007, **9**, 1789.
14. M. Vuilhorgne, J. Malpart, S. Mutti, and S. Mignani, *J. Heterocycl. Chem.*, 2003, **40**, 159.